Periodic Paralysis Associated with Hyperthyroidism

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FORTY-ONE CASES of periodic paralysis associated with hyperthyroidism have been reported[29,30] since Rosenfeld's description in 1902.[30] The periodic paralysis associated with hyperthyroidism is quite similar to the familial type but each type has certain distinguishing characteristics.

Several theories of the pathogenesis of periodic paralysis have been offered. Recent developments in the field of steroid chemistry have resulted in the isolation and identification of the naturally occurring mineralocorticoid called aldosterone. This hormone has been found by Conn[8] and others[1,4,9,12,17,24] to cause a condition called primary aldosteronism which is characterized by spells of paralysis, polyuria, polydipsia and hypertension. The laboratory findings in this condition are essentially hypernatremia, hypopotassemia and metabolic alkalosis.

Conn and associates[7] recently reported that immediately preceding and during an attack of paralysis there is an increase in the rate of aldosterone excretion. Somewhat conflicting information along this line was reported by Jones and associates.[20]

The following is a report of studies that were carried out in the case of a patient with periodic paralysis associated with hyperthyroidism.

REPORT OF A CASE

A 23-year-old Caucasian man was referred to the Communicable Diseases Unit of the Los Angeles County General Hospital in January, 1956, because of flaccid paralysis which had started in the lower extremities and progressed to involve the muscles of the upper extremities and trunk. It had begun only about three hours before admittance, when the patient on attempting to leave a theater found that he could barely walk even with aid. By the time he was admitted to the hospital the paralysis was so severe that the use of a tank respirator was considered. The patient had had no previous attacks. At the time of admission, he denied any symptoms of nervousness or tremor. There was no family history of paralysis.

On physical examination the patient was observed to be normal appearing, well developed, well nourished and somewhat apprehensive. Flaccid paralysis of the lower extremities, the back and the left upper extremity were noted, and there was also slight weakness of the right upper extremity. The blood pressure was 158/50 mm. of mercury, the pulse rate was 120 and the rectal temperature 100.6° F. Deep tendon reflexes were absent in the lower extremities and hypoactive in the upper extremities.

The hemoglobin content was 14.5 gm. per 100 cc. of blood. Leukocytes numbered 9,800 per cu. mm. with the cell differential within normal range. Serum potassium was 2.1 mEq. per liter. The specific gravity of urine was 1.025, the pH was 7.5 and it contained no albumin.

The muscle weakness progressed to involve the right arm and the chest muscles. The vital capacity dropped to about 75 per cent of normal. No abnormalities were noted in the cerebrospinal fluid on two occasions. The patient received supplemental potassium and in 24 hours was able to move all extremities quite well. An electrocardiogram taken 24 hours after the attack showed sinus tachycardia (rate 120) but was otherwise within normal limits. Over the following seven days the serum potassium ranged from 4.5 to 5.9 mEq. per liter and serum sodium values ranged from 150 to 157 mEq. per liter. There was no clinical evidence of hyperthyroidism on this admission other than the tachycardia. An attempt to precipitate an attack of paralysis by exercise, intravenous glucose and insulin was unsuccessful.

Table 1 gives the results of further studies made during a period between attacks of paralysis.

The patient was discharged with instructions to take 80 mEq. of supplemental potassium per day in divided doses. In spite of this dose of potassium the patient had a second attack of paralysis six weeks later. About the time of this attack, symptoms and laboratory data became consistent with hyperthyroidism. Uptake of radioiodine in 24 hours was 72 per cent and the protein bound iodine content was 13.1 micrograms per 100 cc. The result of a second radioiodine uptake test was 71 per cent in 24 hours. A scintogram showed a slightly enlarged thyroid gland with diffuse distribution of the radioactive iodine.

The next paralytic attack occurred in April 1956. At that time two consecutive 24-hour samples, starting six hours before the onset of paralysis, were obtained for assay of aldosterone content. On the day of attack the patient excreted 24 micrograms of aldosterone per day (normal 1 to 3 micrograms per day) and 25 micrograms of aldosterone on the day following the attack.* This attack occurred even though the patient was taking 160 mEq. of potassium daily.

Two months later the patient had another severe attack. At this time serum potassium and serum sodium were 3.1 and 150 mEq. per liter, respectively. The patient showed no response to 2 mg. of Neostigmin® given intravenously, whereas oral potassium chloride checked the progression of the paralysis. Within four hours he was asymptomatic except for mild residual weakness.

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*Since a high potassium content has been found to increase the aldosterone excretion rate,[22] this patient was studied for this phenomenon after correction of the hyperthyroidism. After the patient had been receiving 160 mEq. of potassium daily for one week, he was found to be excreting 5 and 6 micrograms of aldosterone per 24 hours on successive days.

The patient was observed in three of his five severe attacks. A typical attack usually began between 3 and 5 a.m. after a day of extra exertion and chilling. The patient would awake unable to move his lower extremities and with a feeling "as though a rod was being removed from his thighs and legs." The normal strength of the muscles seemed to gradually disappear, the muscles of the thighs and legs being affected first and most severely. The weakness would then spread centrad to involve the abdomen, and in two instances it involved the upper extremities. All the attacks except the first were related to exertion and chilling. All were relieved with potassium.

Propylthiouracil was given for two months preparatory to operation, and subtotal thyroidectomy was carried out. No spells of muscular weakness have occurred in the three years since the administration of propylthiouracil was started and the patient has remained euthyroid.

METHODS

The alveolar carbon dioxide determinations (Table 1) were made continuously with an infrared CO_2 analyzer[6] as the arterial sample was obtained anaerobically. The pH of this specimen was determined immediately in a blood electrode of a Beckman Model G pH meter. The stimulated saliva was obtained while the patient was chewing paraffin. Sodium and potassium concentrations were measured by a Beckman Model DU flamephotometer. The urinary uropepsin determinations were made on a 2-hour timed specimen collected in the fasting state and analyzed as described by West.[38] Sodium-22 was used to measure the 1-hour and 24-hour exchangeable sodium. The 1-hour sample was used as a measure of the extracellular sodium. Potassium-42 was used to measure the 24-hour exchangeable potassium.

Initial Laboratory Work. The initial laboratory work showed that the patient had a hypopotassemia, a high urine specific gravity with an alkaline pH.

Further Studies. The patient had no evidence of metabolic alkalosis. The salivary ratios of sodium to potassium were within normal limits. The uropepsin excretion rates were all normal, as were the extracellular, intracellular and 24-hour exchangeable sodium values and the exchangeable potassium. The 24-hour urinary creatine was increased.

TABLE 1.—*Results of Laboratory Tests Carried Out Between Attacks of Periodic Paralysis*

Test	Results	Normals
*Alveolar CO_2 (mm. Hg.)	35	35-45
*Arterial pH	7.41	7.35- 7.45
Unstimulated salivary Na/K ratio	0.59, 0.61, 0.58	0.5- 1.5
Stimulated salivary Na/K ratio	0.85, 0.85, 0.65	0.8- 3.0
Uropepsin excretion rate units/hour	12-19	15-40
Extracellular sodium mEq.	2590	
Intracellular sodium mEq.	1100	
Exchangeable sodium (24-hr.) mEq.	3700	
Na_e/wt. mEq. per kg.	44.0	37.8-47.5
Exchangeable potassium (24 hr.)	3435	39.8-62.3
K_e/wt. mEq. per kg.	44.4	
24-hour urinary creatinine gm.	1.90	1.23- 2.11
24-hour urinary creatine gm.	0.62	0.02- 0.34

*Simultaneously obtained.

DISCUSSION

Familial periodic paralysis and the periodic paralysis associated with hyperthyroidism appear to be closely related. Both have similar clinical manifestations and precipitating factors, and they are similar also in the changes in electrolyte metabolism associated with them. Periodic paralysis associated with hyperthyroidism differs in that there is no hereditary relationship. It is limited almost entirely to males[33] and correction of the hyperthyroidism results in a cessation of the paralytic episodes.[11,18,31,37] The defect remains, however, as evidenced by the fact that the paralytic episodes return with the return of hyperthyroidism.[11,26]

Shinosaki[32] was able to increase the severity and frequency of episodes of paralysis with thyroid hormone in six of seven patients with periodic paralysis. On the other hand, Wolf[39] reported six cases of familial periodic paralysis in which the patients were not benefited by potassium but could be maintained free of attacks with thyroid hormone.

At present, reports in the literature differ as to the effect of thyroid hormone on adrenal cortical function. In one study[15] it was reported that the aldosterone excretion rate is normal in thyrotoxicosis. The author has observed that the aldosterone excretion rate may be three times normal in severe hyperthyroidism.

Several studies of the electrolyte metabolism during an attack of periodic paralysis have been reported showing that for one to two days before and on the day of an attack there is a decrease in urine output of water, potassium, sodium and chloride.[10,33] The serum potassium and phosphorus are characteristically low during the attack of paralysis.[7,10,33] As the serum potassium and phosphorus return to normal the paralysis disappears.

The exact reason for the drop in serum potassium in periodic paralysis has not been determined. Biopsy of specimens taken during an attack of paralysis have shown that the muscle potassium is slightly increased.[7] According to Vastola[36] there is a total gain of approximately 130 mEq. of potassium per kilogram of muscle solid, which in the average patient would be approximately a 1,300 mEq. increase in muscle cellular potassium. This figure must be high unless potassium transfers from some source besides the extracellular fluid. The rapid absorption of carbohydrates or the injection of insulin or of epinephrine will result in an increase of the utilization of carbohydrate in the tissues. Insulin and epinephrine also have a glycogenolytic activity on the liver, which would result in a loss of potassium

from the liver location. Conn reported that the sodium and potassium content of muscle in periodic paralysis are both increased above normal in terms of mEq. per kilogram of muscle and that there is a decrease in exchangeable potassium with an increase in the exchangeable sodium. In the case herein reported the exchangeable sodium and potassium were within normal limits for a period between two attacks. If the exchangeable potassium is low and the exchangeable sodium is high in periodic paralysis, this electrolyte shift may well have been produced by intermittently high aldosterone before the attack of paralysis. Further, if the muscle potassium is high and the exchangeable potassium is low, then other tissues than muscle must be deficient in potassium. Further studies would seem indicated.

Patients with primary aldosteronism have been found to have chronic total body deficit of potassium and chloride, a retention of sodium and a metabolic alkalosis as the most pronounced chemical changes. These patients have an increase in exchangeable sodium and a decrease in exchangeable potassium.[9] The increased aldosterone in these cases has its origin in adenomas of the adrenal cortex or in hyperplasia of the adrenal cortex. Removal of the functioning adenoma or hyperplastic gland results in a cure of this condition. Periodic paralysis associated with hyperthyroidism may be distinguished from primary aldosteronism by the history, physical findings and the previously mentioned laboratory tests.

Conn and associates[7] reported that in addition to the electrolyte changes in periodic paralysis there is a decided increase in urinary aldosterone excretion rate for one to two days before the onset of the paralysis. About the time that the paralysis subsides (in a spontaneous attack) the aldosterone secretion rate is below normal. An increase in aldosterone secretion rate also occurred in the attacks induced by glucose and insulin.

In the present case an attack could not be induced factitiously; hence a study of the electrolyte change could not be carried out. The situation which consistently seemed to precipitate an attack in the patient was a combination of strenuous physical exercise and chilling which occurred when he went surf-fishing. The aldosterone excretion rate the day of the attack and for 24 hours afterward was definitely increased above the amount one would anticipate from the effect of potassium chloride in the diet.

Clinical studies on the effect of the injection of aldosterone on electrolyte metabolism have been difficult because of the scarcity of the hormone. Reports in the literature[2,16,23] so far seem to indicate that aldosterone causes retention of sodium, chloride and water, with a variable effect on potassium. So far, not enough of the hormone has been given to produce an attack of paralysis. Dosage levels so far have been about 3,000 micrograms per day. If the aldosterone assay method now in use measures about 1 per cent of the total aldosterone output,[22] then patients with periodic paralysis may well be forming from 3,000 to 20,000 micrograms per day immediately preceding and during an attack. Since the electrolyte changes can be precipitated by the injection of carbohydrates, epinephrine or insulin[13] in normal persons without causing paralysis, the development of a high aldosterone output just before and during an attack in patients with periodic paralysis has considerable significance.

The exact mechanism by which the excretion of aldosterone is controlled under normal conditions is still under investigation in several centers. Studies have shown that the level of the serum potassium[22] and the extracellular volume[3] have very important roles in the regulation of this steroid. From the reports of Newman, Redgate, and Farrell,[28] it appears that the main integrating center for the control of aldosterone secretion is in the midbrain, with the regulating hormone, glomerulotropin, present in the pineal gland. In the disease entity of periodic paralysis associated with hyperthyroidism, it would seem most likely that there is an inborn latent physiological defect in the adrenal cortex or in the midbrain regulating center which under the condition of hyperthyroidism and stress results in an intermittently high secretion rate of aldosterone. The clinical manifestations could then be explained by the influence of aldosterone upon the mineral metabolism resulting in muscle paralysis. Other investigators[19] have suggested that an abnormally sensitive adrenal gland may be a factor in periodic paralysis.

An alternate explanation for the high aldosterone levels in periodic paralysis would be a defect in the muscle tissue which causes hypopotassemia and fluid volume shift which results in a secondary rise in this hormone. Further studies would seem to be needed to establish whether or not larger doses of aldosterone can produce the clinical paralysis acutely without potassium diuresis, or whether aldosterone is increased secondarily to some electrolyte or volume change.

SUMMARY

This is a case report of a patient with periodic paralysis associated with hyperthyroidism who had a remission of the paralysis after subtotal thyroidectomy. The patient was found to have none of the persistent electrolyte defects of primary aldosteronism between attacks of paralysis. The 24-hour exchangeable sodium and potassium were both normal. He was found to have a high excretion rate of aldosterone the day of and the day following an attack of paralysis associated with hypopotassemia.

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